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A Green Synthesis and Antibacterial Activity of *N*-Arylsulfonylhydrazone Compounds

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Abstract: A green method has been developed for the synthesis of *N*-arylsulfonylhydrazones via a simple grindstone procedure. By grinding mixtures of benzensulfonyl hydrazides and a series of aryl aldehydes or ketones in the mortar using L-tyrosine as catalyst, 24 *N*-arylsulfonylhydrazones were synthesized in a few minutes with high yield. All compounds were screened for their antibacterial activities. Most of them exhibit some antibacterial activities especially for 3d, 3l and 3v showing high activity against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: Solvent-free; *N*-arylsulfonylhydrazone; L-Tyrosine; Grindstone method; Antibacterial activities

Introduction

Grindstone chemistry can be regarded as the most efficient and green chemistry technology, and its traditional instrument—the mortar and pestle—was used in the stone age [1]. The first application of this technique was preparation of foods, then its application extended to preparation of minerals, medicines and other types of materials. In 1893, *Ling et al*. first used the grindstone method to synthesize the derivatives of quinhydrone [2]. Up to now, it has been demonstrated that more and more types of synthesis such as Reformatsky reaction [3], Aldol condensation [4], Dieckmann condensation [5], Knevenagel condensation [6], Sonogashira reaction [7] and other reactions [8,9] can be performed competently by the grindstone technique. Compared to a traditional organic reaction, the grindstone method often is more efficient than solution-based methods and in some cases even more selective [10]. Furthermore, it also has many advantages, such as mainly mild conditions, reduced pollution, short reaction time, low costs, effective reproducibility and simplicity in process and handling [11-14]. Thus, the grindstone chemistry gained ever-widening attention in greener organic transformations during the past decades.

N-arylsulfonylhydrazones, a branch of acylhydrazones, serve a key role in medicinal chemistry. They display various biological activities, including anti-tumor [15], antibacterial [16], antiviral [17], anti-inflammatory [18] and as novel inhibitors of IMP-1[19] or carbonic anhydrase [20]. In 2007, the *N*-arylsulfonylhydrazone derivative (*E*)-*N*'-(1-(6-bromo-2-methylimidazo[1,2-a]pyridin-3-yl) ethylidene)-N,2-dimethyl-5-nitrobenzenesulfonohydrazide was reported as a novel p110α inhibitor[21]. In 2014, Çevrimli et al. synthesized a new compound, 2-hydroxy-1-naphthaldehydeethanesulfonylhydrazone, exhibiting excellent antibacterial activities [22]. The synthesis of *N*-arylsulfonylhydrazones is similar with that of *N*-acylhydrazones. It is carried out by reacting arylsulfonylhydrazines with aryl/alkyl aldehydes or ketones under reflux, in presence of Brønsted-Lowry acid catalysts and in protic polar solvents. The process takes from few minutes to several hours. However, these conditions inevitably can produce waste liquid pollution with poor stereoselectivity because a mixture of E/Z diastereomers is often formed. Herein, we report a new grindstone method to synthesize *N*-arylsulfonylhydrazones using tyrosine as catalyst with no environmental pollution and high stereoselectivity (Scheme 1).

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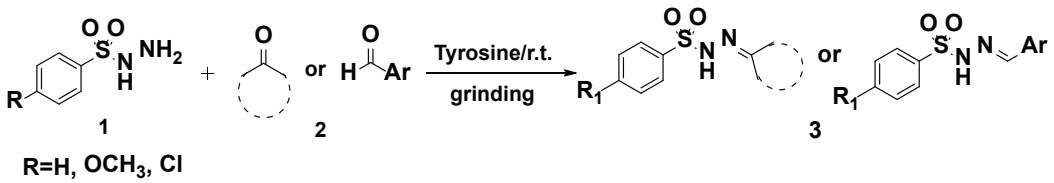


Scheme 1. Synthesis of *N*-arylsulfonylhydrazones by grindstone method.

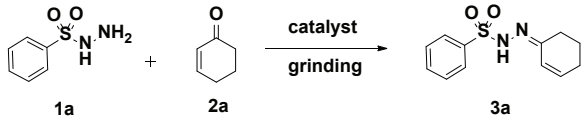
Results and discussion

Chemistry

Initially, according to Pinheiro [23], benzenesulfonyl hydrazine **1a** (1mmol) and 2-cyclohexenone **2a** (1mmol) were ground together in the mortar using 50ul AcOH as catalyst. After 12 minutes, the color of benzenesulfonyl hydrazide gradually changed from light yellow to white, indicating the completion of reaction. The arylsulfonylhydrazone **3a** was isolated (52%) and characterized by NMR and MS (Table 1, entry 1). In order to improve the yield, other catalysts such as $CeCl_3{\cdot}7H_2O$ and K_{10} montmorillonite were tested to get **3a** in 41% and 58% (Table 1, entry 2 and 3). Tyrosine as efficient, bifunctional, and ecofriendly catalyst can catalyze the knoevenagel condensation in high yield [24]. Inspired by this paper, tyrosine was used and obtained **3a** the highest yield ultimately (Table 1, entry 4). Reduction in the amount of L-tyrosine to 10 mol% (Table 1, entry 5) did not show any decrease in the yield and response time. However, the yield was reduced to 50% when the amount of L-tyrosine was cut to 5 mol% and the reaction time was up to 15 minutes, compared to 6 minutes at 10 mol% (Table 1, entry 6). Considering the atom economy of reaction and the yield of **3a**, 10 mol% L-tyrosine was chosen as the appropriate catalyst for this reaction (Table 1, entry 5).

Having obtained the optimized reaction conditions, we investigated the generality of these reaction conditions by extending to a variety of phenyl ring substituted arylsulfonyl hydrazine **1** and ketone or aldehyde derivatives **2.** Thus, grinding **1a** with 2-cyclohexenone **2a** or 2-cyclopentenone **2b** in the mortar at room temperature for 6 minutes, gave yield of 66% of **3a** and 62% of **3b** respectively (Table 2, entry 1 and 2). Similarly, treatment of 2-hydroxyacetophenone **2c** and acetophenone **2d**, gave a higher yield of **3c** 73% and **3d** 78% in a shorter time (Table 2, entry 3 and 4). The similar result occurred from **3e** to **3l** (Table 2, entry 5-12), reacting with the same arylsulfonyl hydrazine **1b** or **1c**, acetophenone **2d** can produce the highest yield (Table 2, entry 8 and 12), followed by **2c** (Table 2, entry 7

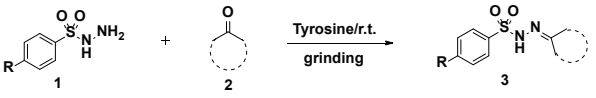
Table 1 Optimization of catalyst type and dosage.[a]



Entry	Catalyst	Catalyst load (mol%)	Time (min)	Yield[b](%)
1	AcOH	50ul	12	52
2	$CeCl_3{\cdot}7H_2O$	15%	10	41
3	K_{10} mont.	15%	10	58
4	L-Tyrosine	15%	6	66
5	L-Tyrosine	10%	6	66
6	L-Tyrosine	5%	15	50

[a]A mixture of 1a (1mmol) and 2a (1mmol) ground in the mortar at room temperature.
[b]Isolated yield.

Table 2 Synthesis of *N*-arylsulfonylhydrazones 3a-3l.[a]



Entry	R	1	2	3	Time (min)	Yield[b] (%)
1	H	1a	2a	3a	6	66
2	H	1a	2b	3b	6	62
3	H	1a	2c	3c	4	73
4	H	1a	2d	3d	4	78
5	OCH_3	1b	2a	3e	6	75
6	OCH_3	1b	2b	3f	6	72
7	OCH_3	1b	2c	3g	4	81
8	OCH_3	1b	2d	3h	2	92
9	Cl	1c	2a	3i	5	78
10	Cl	1c	2b	3j	5	73
11	Cl	1c	2c	3k	4	81
12	Cl	1c	2d	3l	2	84

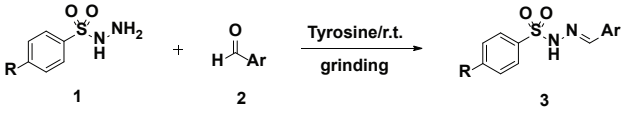
[a]A mixture of 1 (1 mmol) and 2a-2d (1 mmol) ground in the mortar at room temperature using 10% of L-tyrosine as catalyst.
[b]Isolated yield.

and 11), **2a** (Table 2, entry 5 and 9) and **2b** (Table 2, entry 6 and 10). The results showed that electronic factors and steric resistance play as major factors in these reactions. The benzene ring of aryl ketones, equivalent to an electron withdrawing group (EWG), can enhance the formation of a carbocation on the carbonyl group, and further improve the yield of reaction. On the contrary, the electron donating effect of 2-cyclohexenone and 2-cyclopentenone obviously decrease the yield. The steric hindrance of 2-hydroxyacetophenone **2c** may impede the approach of the NH_2 group of the hydrazine to the carbocation on the carbonyl group, which generates a lower yield than acetophenone **2d**. However, the electronic donating group (EDG) at substituent R on the benzenesulfonyl hydrazine cannot cause a significant difference to the yield of **3**, compared to the substrates bearing an electronic withdrawing group (EWG) at R (Table 2, entry 5-12). The main reason is the electronic factors of substituent R have no obvious influence on the nucleophilicity of the NH_2 group of the hydrazine.

As shown in Table 3, aryl aldehydes produce a much higher yield with benzosulfonyl hydrazine because of the their increased reactivity compared to aryl ketones. Different substituents of EDG and EWG attached to the aromatic ring of aryl aldehydes can also lead to a similar result to the one observed with aryl ketones. When benzaldehydes bearing EDG hydroxy are submitted to the grindstone chemistry condensation, easily formatting a carbocation on the carbonyl group, all reactions lead to a higher yield (Table 3, entry 2, 6 and 10). On the other hand, aldehydes bearing EWG chloro- have exhibited a lower yield (Table 3, entry 3, 7 and 11). The reactivity of furfural **2h** is weaker than benzaldehyde leading to the lower yield (Table 3, entry 4, 8 and 12). As described above, for aldehydes or ketones, the ease of formation of the carbonyl carbocation depends upon the nature of the substituents present in the aromatic ring. Electron-donating groups favors its formation, whereas electron-withdrawing substituents exert the opposite effect. Finally, an interesting phenomenon we observed was when furfural **2h**, reacted with *p*-methoxybenzenesulfonyl hydrazine **1b**, the product **3t** was obtained as a mixture of *E*/*Z* diastereomers in a ratio of 1:1. With benzenesulfonyl hydrazine **1a**, the ratio is 2:1. Meanwhile the *E*-isomer can be isolated from the tautomer by recrystallization. However, reacting with *p*-chlorobenzenesulfonyl hydrazine **1c**, the product **3x** was only the *E*-isomer was confirmed by ^{1}H-NMR.

A plausible mechanism for the formation *N*-arylsulfonylhydrazones is depicted in Scheme 2 [24]. L-tyrosine, in its zwitterionic form (**B**), abstracts a proton from the NH_2 group of the benzenesulfonyl hydrazine **(1)** forming the negative ion of hydrazide **(1^1)** which then attacks the protonated benzaldehyde **(2^1)** forming the corresponding intermediate **(2^2)** that loses the water to form the end product **3**.

Table 3 Synthesis of *N*-arylsulfonylhydrazones 3m-3x.[a]



R=H, OCH_3, Cl

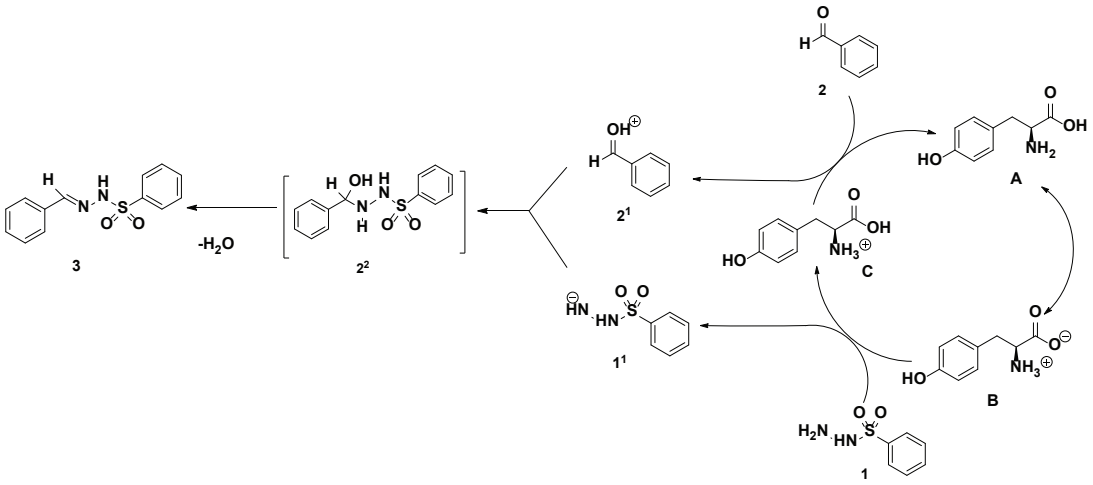
2e=benzalhyde, 2f=o-hydroxybenzaldehyde
2g=p-chlorobenzaldehyde, 2h=furaldehyde

Entry	R	1	2	3	Time (min)	Yield[b] (%)
1	H	1a	2e	3m	4	82
2	H	1a	2f	3n	2	87
3	H	1a	2g	3o	5	78
4	H	1a	2h	3p	6	67
5	OCH_3	1b	2e	3q	4	91
6	OCH_3	1b	2f	3r	2	96
7	OCH_3	1b	2g	3s	4	85
8	OCH_3	1b	2h	3t	6	78
9	Cl	1c	2e	3u	4	88
10	Cl	1c	2f	3v	2	94
11	Cl	1c	2g	3w	4	83
12	Cl	1c	2h	3x	6	66

[a]A mixture of 1 (1mmol) and 2e-2h (1mmol) ground in the mortar at room temperature using 10% of L-tyrosine as catalyst.
[b]Isolated yield.

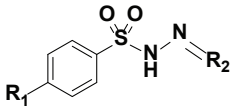
Antibacterial activity

All compounds were screened for their antibacterial activities *in vitro* by broth microdilution method [25] and the minimum inhibitory concentration (MIC) values are presented in Table 4. The antimicrobial drug penicillin was used as reference drug. The results in Table 4 revealed that when the substituent R_1 is OCH_3, the antibacterial activities of *N*-arysulfonylhydrazones were relatively weak (compound 3e, 3f, 3g, 3q, 3r, 3s). Conversely, electron withdrawing group chloro- can increase the antibacterial activity (compound 3i, 3k, 3l, 3u, 3v, 3w, 3x). R_2 has a large influence on the antibacterial activities of *N*-arysulfonylhydrazones compounds. Furaldehyde and acetophenone can enhance the antibacterial activities. Especially for acetophenone, where the MIC of the compounds was found to be the same as that of penicillin against *Staphylococcus aureus* (3d, 3h, 3l). For *p*-chlorobenzaldehyde, the spatial stereo conformation of compounds was changed which may reduce the antibacterial activity.



Scheme 2 Plausible mechanism for the formation of N-arylsulfonylhydrazones.

Table 4 In vitro antibacterial activity of *N*-arysulfonylhydrazones compounds.



R_1=H, OCH_3, Cl
R_2=2-cyclohexenone, 2-cyclopentenone, 2-hydroxyacetophenone, acetophenone,benzalhyde,*o*-hydroxybenzaldehyde, *p*-chlorobenzaldehyde, furaldehyde

Compounds	Minimum inhibitory concentration (ug/mL)[a]	
	Escherichia coli.	*Staphylococcus aureus*
Penicillin	15.6	62.5
3a	62.5	125
3b	125	125
3c	125	125
3d	62.5	62.5
3e	125	125
3f	125	125
3g	125	125
3h	125	62.5
3i	62.5	125
3j	125	>125
3k	62.5	125
3l	62.5	62.5
3m	62.5	125
3n	125	62.5
3o	125	125
3p	62.5	125
3q	125	>125
3r	125	>125
3s	>125	125
3t	62.5	125
3u	62.5	125
3v	62.5	62.5
3w	125	62.5
3x	62.5	125

[a]Results were determined by the broth microdilution method.

Conclusions

In summary, we have described the preparation of *N*-arylsulfonylhydrazones by condensation reaction in solvent free conditions under the grindstone method at room temperature using L-tyrosine as an efficient catalyst. Electronic factors and steric resistance of aryl aldehydes and ketones play key roles in these reactions, which influence the formation of the carbonyl carbocation on carbonyl group, then determine the ease of the reaction. This strategy is useful and attractive for the preparation of *N*-arylsulfonylhydrazones. Antimicrobial screening studies were also performed. The results show that some of the compounds exhibited a good antibacterial activity especially for *Staphylococcus aureus*.

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